UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

30/AUG/2007

MEMORANDUM

Subject: EPA File Symbol: 82542-G **Paraquat Concentrate**
DP Barcode: 339355
Decision No: 377428
PC Code: 061601

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505 P)

MH
Brett T. B
9-30-2007

To: Joanne Miller, RM 25
Herbicide Branch
Registration Division (7505 P)

Applicant: Source Dynamics, LLC
Scottsdale, AZ 85262

FORMULATION FROM LABEL:

Active Ingredient(s):	%
Paraquat dichloride	43.8
Inert ingredients	56.2
Total:	100.0

ACTION REQUIRED: RM requested a review of the acute toxicity data to support the registration of File Symbol #82542-G.

BACKGROUND: Source Dynamics, LLC submitted a pack of six toxicity studies to support the registration of the Paraquat Concentrate. The toxicity studies were conducted at the Product Safety Laboratories, Dayton, NJ.

RECOMMENDATIONS: Each of the six toxicity studies (MRID 47091107-12) is in compliance with the Sub Division F guidelines. These studies are classified as shown in the table (below):

acute oral toxicity	II	acceptable	MRID 47091107
acute dermal toxicity	III	acceptable	MRID 47091108
acute inhalation toxicity	I	acceptable	MRID 47091109
primary eye irritation	I	waived*	
primary dermal irritation	IV	acceptable	MRID 47091110
dermal sensitization study	pos.	acceptable	MRID 47091111

*Note: As per the label claim, and the telephone conversation with the Registrant (8-30-07), TRB has granted a waiver to the eye irritation study.

Labeling:

PRODUCT ID #: 082542-00003

PRODUCT NAME:

PRECAUTIONARY STATEMENTS

SIGNAL WORD: DANGER POISON ☠

SPANISH SIGNAL WORD: PELIGRO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Hazards to Humans and Domestic Animals:

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification. Child Resistant Packaging Required.

Fatal if inhaled. Corrosive. Causes irreversible eye damage. May be fatal if swallowed. Harmful if absorbed through skin. Do not breathe spray mist. Remove and wash contaminated clothing before reuse. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Avoid contact with skin, eyes or clothing. Wear long-sleeved shirt and long pants, socks, shoes, and gloves. Wear: Long-sleeved shirt and long pants, Socks, Shoes, and gloves.

For handling activities, use a non-powered, NIOSH-approved air purifying cartridge respirator equipped with an organic-vapor (OV) removing cartridge plus an N-, R- or P-series filter, OR a non-powered air

purifying canister-type respirator equipped with an organic vapor canister that uses an N-, R-, or P-series air-purifying filter.

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

First Aid:

If inhaled:
-Move the person to fresh air.
-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
-Call a poison control center or doctor for further treatment advice.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a Note to Physician which addresses the category I Acute Inhalation Toxicity, Primary Eye Irritant toxicity. The following statements are suggested types of information that may be included, if applicable:
- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Risk Manager: 25

TYPE OF STUDY: Acute Oral Study in Rats (OPPTS 870.1300, OECD 425)

TEST MATERIAL: Paraquat 43.8% Tech (Paraquat dichloride 48%), dark green liquid, specific gravity =1.157 g/mL

CITATION: Durando, J. (2007). Acute Oral Toxicity Up and Down Procedure-Eurofins/Product Safety Laboratories, Dayton, NJ 08810. Study No. 21077 dated 3-15-07. MRID 47091107. Unpublished

SPONSOR: Source Dynamics, LLC.

EXECUTIVE SUMMARY: LD_{50} of Paraquat 43.8% Tech was determined in an Up and Down Procedure (MRID 47091107) in female SD rats (age 10-12 wks, 185-230g, source: Ace Animals, Boyertown, PA). Based on previous information one animal was initially dosed at 174 mg/kg with the test substance (as received). Additional animals were sequentially dosed at 174, 550 and 1750 mg/kg. Evaluation parameters included signs of gross toxicity and mortality for a subsequent period of 7 and 14 days. Body weights and necropsy findings were recorded on dead/sacrificed animals.

All three animals dosed at 174 mg/kg survived the test. They appeared normal with no clinical signs, and no adverse effects on the weight gains. There were no gross lesions at terminal necropsy. Animals dosed at 550 mg/kg (4 animals) died within 8 days of the test substance administration. Prior to death animals were hypoactive, had reduced fecal volume, soft feces, showed hunched posture/piloerection, and lost body weight. Necropsy of decedents showed discoloration of the intestines and liver.
One animal dosed at 1750 mg/kg died within a day. Clinical signs included hypoactivity. Gross lesions at necropsy showed discoloration of intestines.

The formulation in female rats was 254 mg/kg (approximate 95% C.I =174-550 mg/kg)

Under the conditions of this study the formulation is in EPA Toxicity Category II in terms of oral toxicity.

This study is classified as Acceptable. The study meets the guideline requirement for an acute oral study (OPPTS 870.1100) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Mortality: Several animals died on the study (4 of 4 at 550, and 1 of 1 at 1750 mg/kg).

Three animals dosed at 174 mg/kg survived the test. They appeared normal with no clinical signs, there were no adverse effects on the weight gains.

Animals dosed at 550 mg/kg (4 of 4) died within 8 days of the test substance administration. Prior to death animals were hypoactive, had reduced fecal volume, soft feces, showed hunched posture/piloerection

One animal dosed at 1750 mg/kg died within a day. Clinical signs included "hypoactivity".

A. Necropsy: Necropsy of the decedent (550mg/kg) showed discoloration of the intestine and liver. Animal at 1750 mg/kg showed discoloration of intestines.

D. Reviewer's Conclusions: The product is in EPA Tox Category II, LD_{50} was 254 mg/kg.

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Thursday, August 30, 2007, 8:58:11 AM
Data file name: work. dat
Last modified: 8/30/2007 8:58:06 AM

Test/Substance: Enter test description.
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	3101	174	O	O
2	3102	550	O	X
3	3103	1750	X	X
4	3104	550	X	X
5	3105	174	O	O
6	3106	550	X	X
7	3107	174	O	O
8	3108	550	X	X

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: LR criterion.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
174	3	0	3
550	0	4	4
1750	0	1	1
All Doses	3	5	8

Statistical Estimate based on long term outcomes:

Estimated LD50 = 254 (Based on an assumed sigma of 0.5).
Approximate 95% confidence interval is 174 to 550.

Reviewer: M. Hashim

Date: 8-29-07

Risk Manager (EPA): 25

TYPE OF STUDY: Acute Dermal Toxicity- Rats (OPPTS 870.1200; OECD 402)

TEST MATERIAL: Paraquat 43.8% Tech (Paraquat dichloride 48%), dark green liquid, PSL Reference No. 061026-4G

CITATION: Lowe, C. (2007). Acute Dermal Toxicity Study in Rats- Limit Test. Eurofins/Product Safety Laboratories, Dayton, NJ 08810. Study No. 21078 dated 2-20-07. MRID 47091108. Unpublished

SPONSOR: Source Dynamics, LLC.

EXECUTIVE SUMMARY: Dermal LD_{50} of Paraquat 43.8% Tech was determined in a limit test (MRID 47091108) in SD rats. Ten animals, 5/sex (9-10 wks, wt. males 307-316g, female 209-218g, source- Ace Animals, Boyertown, PA) were treated by topical application of the (undiluted) test material (as received) on 10% of body surface area at 2000 mg/kg. The test site was covered by a gauze pad and secured by a Dura pore tape over the trunk of each animal. Animals were observed for mortality, clinical signs, and behavior changes for 14 days. Weekly body weights and terminal necropsy findings were recorded.

Dermal LD_{50} of the test material in male and/or female rats was >2000 mg/kg

All animals survived the test and gained body weight during the course of the study. There was dermal irritation (edema, erythema /or eschar) in 6 of 10 animals from day 1-14. Four of 10 animals showed irregular respiration, which subsided by day 2. Terminal necropsy findings were not significant.

The product is classified as EPA Tox Category III.

This acute dermal study is Acceptable, it does satisfy the guideline requirements for an acute dermal study in the rat (OPPTS 870.1200; OECD 402).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data confidentiality statements were provided.

RESULTS and DISCUSSION:

Table1. Outcome of the Dermal Study (number died/total numbers)

Dose	Mortality/ Number Tested		
(mg/kg bw)	Male	Female	Combined
2000	0 / 5	0 / 5	0 / 10

A. There were no deaths on the study.

B. Clinical observations: All animals survived the test and gained body weight during the course of the study. There was dermal irritation (edema, erythema /or eschar) in 6 of 10 animals from day 1-14. Four of 10 animals showed irregular respiration, which subsided by day 2.

C. Gross Necropsy - Necropsy findings were unremarkable.

D. Reviewer's Conclusions: The LD_{50} of the test formulation is considered as >2000 mg/kg. The product is in EPA Toxicity Category III in terms of dermal toxicity.

Risk Manager (EPA): 25

TYPE OF STUDY: Acute Inhalation Study in Rats (OPPTS 870.1300, OECD 403)

TEST MATERIAL: Paraquat 43.8% Tech (Paraquat dichloride 48%), dark green liquid, PSl Ref. No. 061026-4G

CITATION: Lowe, C. (2007). Acute Inhalation Toxicity Study in Rats- Limit Test. Eurofins/Product Safety Laboratories, Dayton, NJ 08810. Study No. 21079 dated 3-14-07. MRID 47091109. Unpublished

SPONSOR: Source Dynamics, LLC.

EXECUTIVE SUMMARY: The LC_{50} of Paraquat 43.8% Tech was determined in an acute inhalation (nose only) limit test in SD rats (MRID 47091109). Five rats/sex, m/f (age 9-10 weeks, wt. males- 297-352g, females 226-246g, source-Ace Animals, Inc., Boyertown, PA) were subjected to a single inhalation exposure of the test substance at 0.051 mg/L for 4 hours. The MMAD was 2.15 µm (GSD 2.08). Animals were observed for behavioral changes and signs of toxicity for the duration of study. Body weights and terminal necropsy findings were recorded.

LC_{50} male / female rats was < 0.051 mg/L (gravimetric)

Nine of 10 animals died within 4 days of inhalation exposure, and one animal was euthanized for humane reasons (emaciated/moribund). Within a day clinical signs in rats were abnormal respiration, facial staining, hypoactivity, piloerection/reduced fecal volume. Gross necropsy of the decedents (including moribund animal) showed discoloration of lungs/intestines, edema of lungs, gaseous distension of intestines, and rigor mortis (not related to the test).

The acute inhalation study is Acceptable. It does satisfy the guideline requirements of an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat. The formulation is in EPA Toxicity Category I by the inhalation exposure route.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Table 1. Mortality / Total No. of Animals

Mean achieved atmosphere concentration mg/L	MMAD µm	GSD	Mortality/Number Tested		
			male	female	total
0.05	2.15	2.08	5/5	5/5	10/10*

* includes a moribund animal that was euthanized.

Test Atmosphere / Chamber Description:

Gravimetric Conc.	0.05
Chamber size	6.7. L
Total air flow mean	25.7
Chamber tube Temperature:	21-23^0 C
Relative humidity:	35-38%

Particle size determination was made by multi stage cascade impactor

A. Mortality – Nine of 10 animals died within 4 days of inhalation exposure, and one animal was euthanized for humane reasons (emaciated/moribund), Table 1.

B. Clinical observations: Within one day of exposure rats showed abnormal respiration, facial staining, hypoactivity, piloerection/reduced fecal volume.

C. Necropsy - Gross necropsy of the decedents (including moribund animal) showed edema of lungs, discoloration of lungs/intestines, gaseous distension of intestines.

D. Reviewer's Conclusion: The test substance is of high toxicity (LC_{50} is < 0.051 mg/L) in rats. The formulation is classified as Toxicity Category I.

Reviewer: Masih Hashim Date: 8-29-07

Risk Manager (EPA): 25

TYPE OF STUDY: Primary Skin Irritation Study (OPPTS 870.2500, OECD 404)

TEST MATERIAL: Paraquat 43.8% Tech (Paraquat dichloride 48%), dark green liquid, pH 3.98 (1% w/w solution)

CITATION: Lowe, C. (2007). Primary Dermal Irritation Study in Rabbits. Eurofins/Product Safety Laboratories, Dayton, NJ 08810. Study No. 21081 dated 2-20-07. MRID 47091110. Unpublished

SPONSOR: Source Dynamics, LLC.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47091111), 3 young adult NZW rabbits (sex- male, source: Robinson Services, Clemmons, NC) were topically treated with 0.5 mL of Paraquat 43.8% Tech for 4 hours. Initially one rabbit was treated by applying on 3 treatment sites and removing patches at 3 minutes, one hour, and four hours. Each test site was covered with a gauze pad and wrapped around the trunk by a semiocclusive Micropore tape. All test sites were evaluated for corrosion one hour after patch removal. Subsequent evaluations were performed at 24, 48 and 72 hours after the patch removal. Additional 2 rabbits were treated for 4 hours. After removing the patch / dressing, the irritation was scored by Draize Method for 72 hours.

Application of the test material caused in the first animal unthrifty appearance, (colored) nasal discharge, and excessive salivation. There was no dermal irritation at 3 minute exposure site. Very slight erythema was noted at 1 hour post exposure site, an hour after patch removal. Erythema cleared from this site by 72 hours. Two additional animals at in the second phase showed very slight erythema and very slight edema at 4-hr exposure sites. Animals were free from irritation by 72 hours.

Under the conditions of this study, the test article is slightly irritating to the rabbit skin. The test article is in EPA Tox Category IV.

This study is classified as Acceptable. It does satisfy the guideline requirement of a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations - Application of the test material caused in the first animal unthrifty appearance, (colored) nasal discharge, and excessive salivation. There was no dermal irritation at 3 minute exposure site. Very slight erythema was noted at 1 hour post exposure site, an hour after patch removal. Erythema cleared from this site by 72 hours.

Two additional animals at in the second phase showed very slight erythema and very slight edema at 4-hr exposure sites, one hour after patch removal. Animals were free from irritation by 72 hours. The PDII was 1.0.

B. Results - See table below.

Table 1. Skin Irritation incidence (No. of rabbits with lesion/total No.)

Animal No	erythema	edema	mean score*
=< I hr	3/3	3/3	2.0
24 hrs	3/3	0/3	1.0
48 hrs	3/3	0/3	1.0
72 hrs	0/3	0/3	0.0

*severity

C. Reviewer's Conclusions: The test formulation is in EPA Toxicity Category IV for dermal irritation..

Risk Manager (EPA): 25

STUDY TYPE: Dermal Sensitization – Guinea pig; (OPPTS 870.2600)

TEST MATERIAL: Paraquat 43.8% Tech (Paraquat dichloride 48%), dark green liquid

CITATION: Lowe, C. (2007). Dermal Sensitization Study in Guinea Pigs. Eurofins/Product Safety Laboratories, Dayton, NJ 08810. Study No. 21082 dated 2-12-07. MRID 47091111. Unpublished

SPONSOR: Source Dynamics, LLC.

EXECUTIVE SUMMARY : A Buehler study (MRID 47091111) was performed to assess the sensitization potential of Paraquat 43.8% Tech in guinea pigs. Thirty albino guinea pigs, 20 test and 10 controls (Hartley, 313-436g adult male, source: Elm Hill Breeding Labs, Chelmsford, MA) were used for the test. Twenty animals were topically applied with (0.4 ml) of the undiluted test material for 6 hours, once a week for 3 consecutive weeks through the induction period. Due to severity of irritation 0.4 mL 80% w/w test material in distilled water was used for second and third inductions. Twenty seven days after the first induction, 0.4 ml (HNIC)[+] of the test material (diluted to 12% w/w mixture in distilled water) was applied as a challenge dose to the naïve skin site of each guinea pig. Controls were only exposed to the challenge dose as 12% w/w mixture of the test material in distilled water. The test and control animals were evaluated for dermal reaction (erythema) at 24 and 48 hours after the challenge dose.

According to the text report, six of 20 test animals died before the challenge phase. Prior to death these animals were hypoactive and had irregular respiration / unthrifty appearance. Four out of 8 surviving test animals were hypoactive after the induction phase.

Six of 14 test animals showed faint erythema at 24 and 48 hours after the challenge dose. Very faint erythema was noted for most other sites after the challenge dose. Six of 10 naïve control animals showed very faint erythema at 24 hours following the challenge dose, with irritation persisting through 48 hours in 3 of 10 animals.

Historical positive controls showed appropriate results, and the test was conducted within six months as required.

The test substance is a contact sensitizer.

COMPLIANCE: This study is Acceptable. It does not quite meet the guideline requirement of a sensitization study (OPPTS 870.2600) in the guinea pig. GLP signed papers were provided.

+ highest non irritating concentration in the screening test.

PROCEDURE: A Buehler study (MRID 47091111) was performed to assess the sensitization potential Paraquat 43.8% Tech in guinea pigs. Thirty albino guinea pigs, 20 test and 10 controls (Hartley, 313-436g adult male, source: Elm Hill Breeding Labs, Chelmsford, MA) were used for the test. Twenty animals were topically applied with (0.4 ml) of the undiluted test material for 6 hours, once a week for 3 consecutive weeks through the induction period. Due to severity of irritation only 80% w/w test material in distilled water was used for second and third inductions. Twenty seven days after the first induction, 0.4 ml $(HNIC)^{+}$ of the test material (diluted to 12% w/w mixture in distilled water) was applied as a challenge dose to the naïve skin site of each guinea pig. Controls were only exposed to the challenge dose as 12% w/w mixture of the test material in distilled water. The test and control animals were evaluated for dermal reaction (erythema) at 24 and 48 hours after the challenge dose.

A. Induction – Test material 100%, then 80% (w/w in distilled water) following the first induction.

B. Challenge - Topical- 12% w/w test material in distilled water.

C. Controls - 10 animals- 12% w/w mixture in distilled water.

D. Positive Control- Historical control (HCA) 75% w/w mixture in mineral oil (10-11-06). This positive control as referenced was conducted within six months of the main study.

II. RESULTS and DISCUSSION:

Six of 20 test animals died before the challenge phase. Prior to death these animals were hypoactive and showed irregular respiration / unthrifty appearance. Four out of 8 surviving test animals were hypoactive after the induction phase.

	Test group	Control group
Positive	6/14 animals (24/48 hrs)	6/10 animals (24 hrs) and 3/10 animals (48 hrs)

According to the report text six of 14 test animals showed faint erythema 24 and 48 hours after the challenge dose. Very faint erythema was noted for most other sites after the challenge dose.
Six of 10 naïve control animals showed very faint erythema at 24 hours following the challenge dose, irritation persisting through 48 hours in 3 of 10 animals.

Historical positive controls showed appropriate results.

Reviewer's Conclusions: The test substance is a contact sensitizer.

ONE LINER:
Barcode: 339355
Date: TEST MATERIAL:

Study/ Species/ Lab/ # / date	MRID	Results	Tox. Cat	Core Grade
Acute oral toxicity/rat/Product Safety /21077/ 3-15-07	47091107	Oral LD_{50} is 254 mg/kg females	II	A
Acute dermal toxicity/rat/ Product Safety Lab/ # 21078/ 2-20-07	47091108	Dermal LD_{50} is > 2000 mg /kg, m/f	III	A
Acute inhalation toxicity/rat/ Product Safety/ 21079/ 3-14-07	47091109	LC_{50}<0.051 mg/L males/females	I	A
Dermal irritation/ rabbit/ Product Safety Lab/ 21081/ 2-20-07	47091110	Mild irritant PDII 1.0	IV	A
Dermal sensitization/ guinea pig/ Product Safety/ #21082/ 2-12-07	47091111	contact sensitizer	-	A